REMARKS

The Office Action and the cited and applied reference have been carefully reviewed. No claim is allowed. Claims 93, 95 and 98-120 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claim 118 has been rejected under 35 U.S.C. §112, first paragraph, because the examiner holds that the specification, while being enabling for claims limited in scope to a monoclonal antibody specifically recognizing a polypeptide of SEQ ID NO:2, wherein Xaa is Met or Thr, does not reasonably provide enablement for claims to a monoclonal antibody to any or all "interferon-γ inducing protein". Claim 118 is now amended to recite that the monoclonal antibody recognizes the polypeptide having the amino acid sequence of SEQ ID NO:2, wherein Xaa is Met or Thr, thereby obviating this rejection.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 93, 95 and 98-120 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Nakamura et al., *Infect. Immun.* 61:64-70 (1993). The examiner states that the applicant's arguments are not persuasive and indicates that the post filing date reference by Okamura confirms that IGIF in the serum sample (the 75 kDa, Nakamura, 1993) was proved to be the same IGIF as that found in the liver extract (19 kDa), and it was considered to be bound to another protein or to exist in an oligomeric form (page 3969, the second paragraph of the left column). The examiner further states that

it is irrelevant as to how or what Dr. Okamura considered the "factor" might or might not be originally, as the fact is that Nakamura's "factor" is the same as that of the present invention as disclosed in the later Okamura reference. This rejection is respectfully traversed.

Applicants disagree with the examiner that the later Okamura reference confirms that the IGIF in the serum sample (75 kDa, Nakamura, *Infect. Immun.* 61:64-70, 1993) was proved to be the same IGIF as that found in the liver extract (19 kDa). The later Okamura reference does not confirm such thing; the Okamura reference only confirms that IGIF, which was purified and isolated in the Okamura reference, was just contained in serum sample ("factor"), but never confirmed that IGIF is the same as the "factor" disclosed in the Nakamura reference. In fact, the Okamura reference states at page 3971, in the paragraph bridging the left and right columns:

> The amino acid sequence of the NH2-terminal portion of this protein was determined and shown to be *a novel protein*. Unexpectedly, the IGIF that was previously found in the sera of mice and that caused endotoxic shock (16, 17) was shown to *contain the same molecule as was purified from the liver extract* (Fig. 5). (emphasis added)

Thus, as described above, IGIF is a novel protein which was found by the authors of the Okamura reference, a reference which was published after the cited and applied Nakamura reference. It is clear then that Nakamura did not recognize even the presence of IGIF and did not succeeded in isolating IGIF. Therefore, applicants believe that it is unreasonable to consider that the "factor" of the Nakamura reference is

the same as the IGIF of the Okamura reference, even if the 75 kDa "factor" contains IGIF (19 kDa).

> Furthermore, the Okamura reference states as follows:
>
> ... it was considered to be bound to another protein or to exist in an oligomeric form. (page 3969, left column, lines 24-25)
>
> "Therefore, this apparently L-12 like factor in serum was demonstrated to be a distinct molecule from IL-12, whose molecular mass is 75 kDa. However, the molecular form of IGIF in the serum remains unknown. It may exist in an oligomeric form or may be bound another molecule. (page 3971, right column, lines 4-8; emphasis added)

Thus, it is clear from these disclosures that the "factor" of Nakamura reference is not same as the IGIF of the Okamura reference because IGIF "*may exist in an oligomeric form or may be bound another molecule*", even if it was contained in the "factor" of Nakamura reference. It is apparent that IGIF exists in an oligomeric form or is bound by another molecule which is not same as IGIF *per se*.

In addition, as applicants have repeatedly pointed out, there are various physicochemical differences between IGIF of the Okamura reference and the "factor" of the Nakamura reference. A summary table of the differences is presented below:

	IGIF of Okamura reference	"factor" of Nakamura reference
origin	liver of mouse	serum of mouse
molecular weight	19,000 ± 5,000 Da (SDS-PAGE)	50,000 ~ 55,000 Da (SDS-PAGE)
activity	will not lose its activity when treated with SDS-PAGE	will lose its activity when treated with SDS-PAGE

As mentioned above, IGIF "may exist in an oligomeric form or may be bound another molecule", even if it was contained in the "factor" of the Nakamura reference. Therefore, applicants submit that it would have been difficult at the time the present application was filed to reasonably expect that a monoclonal antibody or antibody which recognizes IGIF or IL-18 can be obtained using the "factor" of Nakamura, because IGIF had not been isolated by Nakamura even if IGIF was contained in Nakamura's "factor".

By contrast, the applicants have succeeded in isolating IGIF and then, using the isolated IGIF, obtained an "isolated" monoclonal antibody which recognizes IGIF or IL-18. Applicants have amended the claims to insert the term "isolated" before "monoclonal antibody" in order to make this clear. Furthermore, the Nakamura reference states on page 69, left column, lines 8-12:

> However, details of the molecule such as its terminal amino acid sequence or amino acid composition to be compared with details of the known cytokines remain to be elucidated. *We were unable to obtain sufficient amounts of the factor for these purposes*. (emphases were added)

In the light of the state of the art at the time the Nakamura reference was published, several µg or more protein was needed to determine terminal amino acid sequence or amino acid composition.

At the time the present application was filed, more than 10µg of protein was needed to obtain a monoclonal antibody of a protein (please see Example 3-3 of the present specification). A copy of Lochner et al., *Journal of Immunological Methods*, 259:149-157 (2002) is attached hereto to show that such an amount was needed. As described

at page 150, right column, section "2.3 Immunization of IL-18-deficient mice", 10 µg rmIL-18 was used.

It is clear that at the time the Nakamura reference was published, the technique to obtain sufficient amounts of the "factor" had not been established. In particular, mouse serum is not an appropriate source of the "factor". In fact, the Okamura reference states on page 3967, right column, lines 4-5 from the bottom that "Since it was difficult to get enough of the factor from serum to analyze, liver extracts were examined."

In view of this disclosure, it can be said that it would have been difficult at the time the present application was filed to obtain a monoclonal antibody of IGIF or IL-18 from the disclosure of the Nakamura reference, because Nakamura teaches nothing about preparing sufficient amounts of Nakamura's "factor". Without a sufficient amount of Nakamura's "factor", a monoclonal antibody which recognizes IGIF or IL-18 would have been difficult to obtain by one of ordinary skill in the art even if IGIF or IL-18 were to be contained in Nakamura's "factor" and even if a method for obtaining monoclonal antibody of a protein was established at the time the present application was filed.

Moreover, even at the time the Okamura reference was published, a monoclonal antibody of IGIF had still not been obtained (see page 3972, left column, first paragraph).

Accordingly, the cited and applied Nakamura reference cannot make obvious the presently claimed invention.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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